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| 10/509,095 | 04/13/2005 | Manfred Windisch | 4301-1117 | 4495 |

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| WANG, CHANG YU | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1649 | |

DATE MAILED: 10/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/509,095 | WINDISCH, MANFRED | |
| | Examiner | Art Unit | |
| | Chang-Yu Wang | 1649 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *07 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *4,5 and 10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6-9 and 11-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/28/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Status of Application Election/Restrictions*

Applicant's election with traverse of Group VIII and species of proline substitution on both N-terminal and C-terminal in the reply filed on August 7, 2006 is acknowledged. The traversal is on the ground(s) that all of the claims share the same special technical feature and depend from generic claim 1. In addition, Applicant argues that at least 10 polynucleotide sequences can be examined without restriction. Further, Applicant argues that the International Search Authority did not determine lack of unity for the same set of the claims. Applicant argues that Group I should include SEQ ID NOS: 1-11 with a basis sequence of KEGV, Group II should include SEQ ID NOS: 12-22 with a basis sequence of MDVF, Group III should include SEQ ID NOS: 23-33 with a basis sequence of DVF, Group IV should include SEQ ID NOS: 34-40 with a basis sequence GL and Group V should include SEQ ID NOS: 41-46 with a basis sequence of LS. Applicant further argues that the species election of proline substitution does not change the formal characteristics of the peptide.

Applicant's arguments have been fully considered but they are not found persuasive. Since SEQ ID NO:I is known in the art as disclosed in W0 01/60794, it does not have a special technical feature. Therefore, claim 1 does not recite a special technical feature, defined by the PCT rules as a feature that defines a contribution over the prior art. Since the 1st claimed invention has no special technical feature, it cannot share a special technical feature with the other claimed inventions. Thus, Applicant's inventions do not have a single inventive concept and so lack unity of invention.

In addition, based on MPEP §803.04, USPTO allows 10 independent nucleic acid sequences without restriction for search in one application, which is not applied to amino acid sequences because of the complexity and function of amino acid sequence. In addition, although some of SEQ ID NOs:1-46 share a basis sequence, each peptide has different compositions and a unique structure, which would not generate the same activity as those with different length and amino acid sequences. Thus, the outcome of using a sequence of SEQ ID NO: 1 would not be predictably same as that of using SEQ ID NO:11 in a method of screening an agent or treating a disease. Accordingly, a peptide comprising an amino acid sequence of any of SEQ ID NO:1-46 does not share a common special technical feature with each other. Further, the practice of USPTO in determining whether Applicant's inventions lack an inventive concept of unity is not bound to the decision made by the International Search Authority. Moreover, each substitution with a different amino acid in a peptide is patentably distinct because the substitution on the peptide changes the biochemical property of the peptide. However, the requirement of proline substitution at N-, C-terminus or at both N-and C-terminus is withdrawn.

The requirement for the rest of restriction is still deemed proper and is therefore made FINAL.

Claims 1-24 are pending. Claim 10 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Claims 1-9 and 11-24 are under examination in this office action.

### *Priority*

Should applicant desire to obtain the benefit of foreign priority under 35 U.S.C. 119(a)-(d) prior to declaration of an interference, a translation of the foreign application should be submitted under 37 CFR 1.55 in reply to this action.

### *Specification*

The disclosure is objected to because of the following informalities: The sequences listed on p. 9, 13-14, tables 1-2 required sequence identifiers. Appropriate correction is required.

### *Claim Objections*

Claims 1-9 and 11-24 are objected to as encompassing non-elected sequences.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a peptide comprising the amino acid sequence of SEQ ID NO:8, does not reasonably provide enablement for any peptide comprising any amino acid sequence of SEQ ID NO:8 as broadly claimed. The specification does not

enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

"There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is 'undue'. These factors include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

*In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)". See MPEP § 2164.01.

Claims 1-9 are directed to a peptide comprising an amino acid sequence of SEQ ID NO:8 or an amino acid sequence of SEQ ID NO:8 with a proline substitution at the N- and C-termini or aceylation or amidation.

The nature of the instant invention is based on the activity of blocking the interaction of amyloid-beta with β-synuclein by the amino acid sequence of the core

domain of β-synclein (1-15 amino acids) that interacts with amyloid-beta. Applicant describes that a peptide consisting of the amino acid sequence of SEQ ID NO:8 has neuroprotective effects on neurons in vitro with conditions of serum withdrawal, addition of ionomycin, chronic stress of iron chloride/hydrogen peroxide and apoptosis caused by amyloid-beta aggregation. However, Applicant fails to provide sufficient guidance as to whether any peptide comprising any amino acid sequence of SEQ ID NO:8 can preserve the neuroprotective activity of the SEQ ID NO:8. The art recognizes that while many amino acid substitutions are possible in any given protein, the position of where such amino acid substitutions can be made is critical for maintaining the function of a protein; i.e. only certain positions can tolerate conservative substitutions without changing the relationship of three dimensional structure and function of the protein (col 2, p. 1306, Bowie et al. Science, 1990, 247:1306-1310). It has been shown that a single amino acid change can alter the function of a protein. For example, a substitution of lysine residue by glutamic acid at position 118 of acidic fibroblast growth factor results in a substantial loss of its biological activity including the binding ability to heparin and its receptor (Burgess et al. J of Cell Bio. 111:2129-2138, 1990).

The specification only describes several peptides on p 4-5 of the specification, the specification fails to teach other peptides comprising an amino acid sequence of SEQ ID NO:8 or an amino acid sequence of SEQ ID NO:8 with proline modification or acylation, or amidation at N- or/and C-termini. There is no identification of what other particular portion of the peptide structure that must be conserved. Applicant fails to teach what other common regions are required for a peptide comprising an amino acid

sequence of SEQ ID NO:8 to maintain the characteristics or activity of SEQ ID NO:8. There is no guidance as to what could be changed and what could not be changed to preserve any common characteristics of SEQ ID NO:8 that function as SEQ ID NO:8. In addition, the specification does not provide guidance as to how to make and use this broad genus. Although Applicant describes some possibilities of amino acid substitution/modification in the specification, Applicant does not provide sufficient guidance as to what other amino acids can be included/not included in these peptides to maintain any structural or functional activity or specificity like SEQ ID NO:8. It has been shown that a change of amino acid sequence results in the change of the protein conformation, which consequently changes the binding ability of the peptide to its binding partner or receptors. In addition to a core determinant sequence, the protein-protein interaction also relies on the flanking or noncontiguous residues (see p. 445 the second column, first paragraph, Pawson et al. 2003, Science 300:445-452). The optimal binding motif for a domain is not necessarily suitable for physiological or in vivo interaction. The predictive data always need to be validated by actual analyses in cells (see p. 445, the third column, second paragraph, Pawson et al. 2003, Science 300:445-452). Applicant fails to provide sufficient guidance as to what other regions of the claimed peptides are required in order to preserve the functional activity of SEQ ID NO:8. A skilled artisan cannot predict the function/activity of these claimed peptides without knowing what other structures and whether other structures would affect the activity of SEQ ID NO:8 in neuroprotection. Thus it is unpredictable whether these

claimed peptides can function as SEQ ID NO:8, indicating that undue experimentation is required to practice the claimed invention.

Therefore, in view of the necessity of experimentation, the limited working examples, the unpredictability of the art, and the lack of sufficient guidance in the specification and the lack of knowledge of function for each sequence, one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention as it pertains to a peptide comprising an amino acid sequence of SEQ ID NO:8 or an amino acid sequence of SEQ ID NO:8 with proline modification or acylation, or amidation at N- or/and C-termini.

Claims 11-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 11-24 are directed to pharmaceutical composition comprising a peptide comprising an amino acid sequence of SEQ ID NO:8 or an amino acid sequence of SEQ ID NO:8 with proline modification or acylation, or amidation at N- or/and C-termini. Claims 11-24 are not enabled for the reasons as set forth above. In addition, Applicant fails to provide sufficient guidance as to enable on of skill in the art to practice the claimed invention. Based on the specification, Applicant is enabled for protecting neuronal cell death from serum withdrawal, oxidative stress, apoptosis caused by

amyloid-beta aggregation in vitro. However, claims 11-24 are directed to a pharmaceutical composition comprising a peptide comprising an amino acid sequence of SEQ ID NO:8 for treating diseases associated with free radical, hypoxia, ischemia, and neurodegenerative diseases. Applicant fails to provide any guidance or working example as to enable one of skill in the art to treat any pathological conditions as recited in the claims 11-14. Although β-synuclein has been shown to be a negative regulator for α-synuclein aggregation and has been suggested to be used as a strategy to treat neurodegenerative diseases (Hashimoto, et al. Neuron 2001. 32: 213-223), Applicant fails to demonstrate the results derived from in vitro can reproduced in treating diseases in vivo as recited in claims 11-14 since the in vivo system is more complex than the well-controlled in vitro condition. The in vivo condition involves the efficacy, penetration, targeting and stability of the peptide in a biological system. In addition, different diseases have different causes and underlying molecular mechanisms. Applicant describes that 21 of the 45 peptides examined showed neuroprotective potential. However, Applicant fails to provide sufficient guidance or any working example to teach how to use the claimed invention in treating the diseases as recited in claims 11-14 and whether the claimed peptide is effective in treating the diseases. Accordingly, it would appear that Applicant provides a finding, and then presents an invitation to experiment to determine whether these peptides are useful for treating the diseases as claimed and determine how to use the peptides to treat patients with the. To practice such an invention would require knowledge of how to use the peptides to treat the patients with the guidance of the route, duration and quantity of administration of a peptide to a

subject and this information is not provided by the instant specification. The instant specification, as filed, provides insufficient guidance or no working example as to enable one skilled in the art to practice the claimed invention as recited in claims 11-24, thereby requiring undue experimentation to discover how to use Applicant's invention, as currently claimed.

In addition, In the absence of this guidance a practitioner would have to resort to a substantial amount of undue experimentation involving the variation in the amount and duration of administration of a peptide of the instant invention and in determining a suitable route of administration and evaluate whether the peptide is effective in treating any pathological condition as recited in the claims. Thus, it is unpredictable whether the claimed pharmaceutical composition can treat any disorder as recited in the claims. Therefore, in view of the necessity of experimentation, the limited working examples, the unpredictability of the art, and the lack of sufficient guidance in the specification, one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention. The instant specification is not enabling for the claimed pharmaceutical compositions in treating a pathological condition as recited in claims 11-24 because one skilled art can not following the guidance presented therein and practice the claimed invention without first making a substantial inventive contribution.

Claims 1-9 and 11-24 are further rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way

as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

Claims 1-9 are directed to a peptide comprising an amino acid sequence of SEQ ID NO:8 or an amino acid sequence of SEQ ID NO:8 with proline modification or acylation, or amidation at N- or/and C-termini. Claims 11-24 are directed to a pharmaceutical composition comprising a peptide comprising an amino acid sequence of SEQ ID NO:8 or an amino acid sequence of SEQ ID NO:8 with proline modification or acylation, or amidation at N- or/and C-termini. The specification only describes several peptides on p 4-5 of the specification, the specification fails to teach other peptides comprising an amino acid sequence of SEQ ID NO:8 or an amino acid sequence of SEQ ID NO:8 with proline modification or acylation, or amidation at N- or/and C-termini. However, the claims are not limited to only a peptide comprising the amino acid sequence of SEQ ID NO:8 ; rather the claims encompass a genus of a peptide comprising any amino acid sequence of SEQ ID NO:8. Thus, the claims encompass a genus of a peptide comprising an amino acid sequence of SEQ ID NO:8 or an amino

acid sequence of SEQ ID NO:8 with proline modification or acylation, or amidation at N- or/and C-termini.

In making a determination of whether the application complies with the written description requirement of 35 U.S.C. 112, first paragraph, it is necessary to understand what Applicant has possession of and what Applicant is claiming. From the specification, it is clear that Applicant has possession of a peptide comprising the amino acid sequence of SEQ ID NO:8 and β-synuclein. However, Applicant is not in possession of all peptides comprising any amino acid sequence of SEQ ID NO:8. or any amino acid sequence of SEQ ID NO:8 with proline modification or acylation, or amidation at N- or/and C-termini. Applicant fails to teach what other common structures/characteristics are required for a peptide comprising an amino acid sequence of SEQ ID NO:8 or an amino acid sequence of SEQ ID NO:8 with proline modification or acylation, or amidation at N- or/and C-termini.

The specification only describes several peptides in the specification but fails to teach what other common structures/characteristics/features are required for other peptides comprising an amino acid sequence of SEQ ID NO:8 or an amino acid sequence of SEQ ID NO:8 with proline modification or acylation, or amidation at N- or/and C-termini to preserve the activity of SEQ ID NO:8. There is no identification of what other particular portion of the peptide structure that must be conserved. The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the claimed genus of peptides. While a generic sequence is provided, there is merely a set of common properties: there is no

description of the conserved regions which are critical to the function of the genus claimed. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify peptides encompassed. Applicant fails to describes/specify what other common structures/characteristics that are required for a peptide comprising an amino acid sequence of SEQ ID NO:8 or an amino acid sequence of SEQ ID NO:8 with proline modification or acylation, or amidation at N- or/and C-termini to preserve the function of SEQ ID NO:8. Thus, a skilled artisan cannot contemplate the functional relationship between the above genus and the claimed invention.

Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the genus of proteins used in the claimed methods.

*Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until

reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, a peptide comprising an amino acid sequence of SEQ ID NO:8 or an amino acid sequence of SEQ ID NO:8 with proline modification or acylation, or amidation at N- or/and C-termini and a pharmaceutical composition comprising the peptide have not met the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 14 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 14 is indefinite because Applicant recites "all states" in the claims. Applicant fails to describe what all states similar to the neurodegenerative diseases are. There is no limitation on what would or would not be considered as all states similar to neurodegenerative diseases and thus be within the scope of the claims.

Claim 20 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim is indefinite because Applicant recites "implants" but fails to describes/specify what is encompasses within the implants. The disclosure fails to set for the metes and bounds of what is encompassed within the definition of such implants. It is unclear what implants applicant is intending to encompass and thus the claim is indefinite.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 5 and 7-24 are rejected under 35 U.S.C. 102(b) as being anticipated by WO200160794 (published Aug 23, 2001, PCT/US01/05569, filed Feb 20, 2001, priority date Feb 18, 2000).

WO200160794 teaches a beta-synuclein peptide (1-15 amino acids) for suppression of alpha-synuclein aggregation, which has 100% identity to the instant SEQ ID NO:1 and SEQ ID NO:8. The sequence search results disclose as follows:

```
AAE08565
ID   AAE08565 standard; peptide; 15 AA.
AC   AAE08565;
DT   15-NOV-2001  (first entry)
DE   Human beta-synuclein peptide #1 to suppress alpha-synuclein aggregation.
KW   Human; transgenic mouse; amyloid precursor protein; APP; therapy;
     Parkinson's disease; Alzheimer's disease; alpha-synuclein;
     amylodogenesis; neurodegenerative disease; beta-synuclein.
OS   Homo sapiens.
PN   WO200160794-A2.
PD   23-AUG-2001.
PF   20-FEB-2001; 2001WO-US005569.
PR   18-FEB-2000; 2000US-0183571P.
PA   (REGC ) UNIV CALIFORNIA.
PI   Masliah E;
DR   WPI; 2001-529900/58.
PT   A transgenic mouse comprising nucleotide sequences encoding human amyloid
     precursor protein and human alpha-synuclein useful for identifying
     therapeutic agents for the treatment of Parkinson's disease.
PS   Example 4; Page 53; 55pp; English.
CC   The invention relates to a transgenic mouse comprising transgenic
     nucleotide sequences each operably linked to a promoter and integrated
     into the genome. Each nucleotide sequences encodes human amyloid
     precursor protein (hAPP) and human alpha-synuclein. The invention also
     relates to a method for screening therapeutic agents that inhibit
     amylodogenesis and amyloid deposition associated with neurodegenerative
     disease and alpha-synuclein aggregation. The method is useful for
     modulating expression, production or formation of intraneuronal
     amyloidogenic alpha-synuclein aggregation in a subject. The method is
     also useful for identifying therapeutic agents for the treatment and
     diagnosis of Parkinson's disease and Alzheimer's disease. The present
     sequence is N-terminal region of beta-synuclein peptide (1-15 amino
     acids) for suppression of alpha-synuclein aggregation
  SQ   Sequence 15 AA;

  Query Match             100.0%;  Score 14;  DB 4;  Length 15;
  Best Local Similarity   100.0%;  Pred. No. 7.1e-09;
  Matches   14; Conservative   0;  Mismatches   0;  Indels   0;  Gaps   0;
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Qy          1 DVFMKGLSMAKEGV 14
              ||||||||||||||
Db          2 DVFMKGLSMAKEGV 15

AAE08565
ID   AAE08565 standard; peptide; 15 AA.
AC   AAE08565;
DT   15-NOV-2001  (first entry)
DE   Human beta-synuclein peptide #1 to suppress alpha-synuclein aggregation.
KW   Human; transgenic mouse; amyloid precursor protein; APP; therapy;
     Parkinson's disease; Alzheimer's disease; alpha-synuclein;
     amylodogenesis; neurodegenerative disease; beta-synuclein.
OS   Homo sapiens.
PN   WO200160794-A2.
PD   23-AUG-2001.
PF   20-FEB-2001; 2001WO-US005569.
PR   18-FEB-2000; 2000US-0183571P.
PA   (REGC ) UNIV CALIFORNIA.
PI   Masliah E;
DR   WPI; 2001-529900/58.
PT   A transgenic mouse comprising nucleotide sequences encoding human amyloid
     precursor protein and human alpha-synuclein useful for identifying
     therapeutic agents for the treatment of Parkinson's disease.
PS   Example 4; Page 53; 55pp; English.
CC   The invention relates to a transgenic mouse comprising transgenic
     nucleotide sequences each operably linked to a promoter and integrated
     into the genome. Each nucleotide sequences encodes human amyloid
     precursor protein (hAPP) and human alpha-synuclein. The invention also
     relates to a method for screening therapeutic agents that inhibit
     amylodogenesis and amyloid deposition associated with neurodegenerative
     disease and alpha-synuclein aggregation. The method is useful for
     modulating expression, production or formation of intraneuronal
     amyloidogenic alpha-synuclein aggregation in a subject. The method is
     also useful for identifying therapeutic agents for the treatment and
     diagnosis of Parkinson's disease and Alzheimer's disease. The present
     sequence is N-terminal region of beta-synuclein peptide (1-15 amino
     acids) for suppression of alpha-synuclein aggregation
SQ   Sequence 15 AA;

  Query Match             100.0%;  Score 7;  DB 4;  Length 15;
  Best Local Similarity   100.0%;  Pred. No. 0.2;
  Matches   7;  Conservative   0;  Mismatches   0;  Indels   0;  Gaps   0;

Qy          1 SMAKEGV 7
              |||||||
Db          9 SMAKEGV 15
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WO200160794 also teaches different modifications on the peptide at the C-terminus and acetylation at the N-terminus and amidation at the C-terminus of the peptide to preserve the stability of the peptide (see p. 37, lines 14-20). WO200160794

further teaches several ways of formulation for different administration routes as described as "The formulation of the composition should suit the desired mode of administration. Those of skill in the art are familiar with the principles and procedures discussed in widely known and available sources as Remington's Pharmaceutical Science (1 7th Ed., Mack Publishing Co., Easton, PA, 1985) and Goodman and Gilman's The Pharmaceutical Basis of Therapeutics (8th Ed., Pergamon Press, Elmsford, NY, 1990)", for example intravenous or others including encapsulation in liposomes, microparticles, microcapsules for different administration routes as recited in claims 15-24 (see p. 10, line27 to p.12, line 18; p13, lines 13-20).

The teaching of the 15-amino acid beta-synuclein peptide by WO200160794 meet the limitation of a peptide comprising an amino acid sequence of SEQ ID NO:8 as recited in claims 1-2 because the natural occurring amino acids in proteins/pepetides are L-amino acids and few are D-amino acids after post-translational modification as evidenced by (Volkmann et al. EXS, 1998, 85: 87-105). The teachings of acetylation at the N-terminus and amidation at the C-terminus meet the limitation of modification as recited in claims 7-9. In addition, the intended use for treating diseases as recited in claims 11-14 are not given patentable weight because the peptide encompassed in the composition is the same product with the same structure. A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. Thus, Claims 1, 2, 5, 7-24 are anticipated by WO200160794.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO200160794 (published Aug 23, 2001, PCT/US01/05569, filed Feb 20, 2001, priority date Feb 18, 2000).in view of Volkmann et al. (EXS, 1998, 85: 87-105).

- WO200160794 teaches as set forth above but fails to teach D-amino acids.

Volkman et al. teach D-amino acids provide several advantages for a peptide/protein including increased potency and protease stability and a novel tertiary structure that could not be accessed from L-amino acids (see p.87, abstract). The teachings of Volkman et al. provide a motivation and a reasonable expectation of success to generate a peptide with D-amino acids.

Thus, it would have been obvious for one of ordinary skill in the art at the time of the instant invention was made to generate a β-synucleic peptide that blocks the Ab aggregation by using D-amino acids. The person of ordinary skill in the art would have been motivated to make that modification because it has been shown that D-amino acids can be used to increase the potency and protease stability. One of ordinary skill in the art would have expected success in generate such peptide for the purpose of blocking Aβ aggregation or other pharmaceutical purposes.

Claims 1 and 4-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO200160794 (published Aug 23, 2001, PCT/US01/05569, filed Feb 20, 2001, priority date Feb 18, 2000).in view of Viguera et al. (Protein science 1999. 8:1733-1742) and Prieto et al. (J. Mol. Biol. 1997. 274: 276-288).

WO200160794 teaches as set forth above but fails to teach proline substitution at the N- and C-terminus.

Viguera et al. teach modification of an amino acid in a peptide with proline at N-terminus of the peptide can enhance the stability of the peptide (see p. 1733, abstract; p.1734, 1st col. 3rd paragraph).

Prieto et al. teach modification of an amino acid in a peptide with proline at C-terminus of the peptide can enhance the stability of the peptide (see p. 276, abstract).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the peptide with proline substitution at both N- and C-termini to enhance the stability of the peptide. Since it has been shown that proline substation at N-terminus or C-terminus can enhance the stability of the peptide, the person of ordinary skill in the art would have been motivated to make that modification to enhance the protease/thermal stability of the peptide and prevent the degradation of the peptide in a biological system because a biological system contains a lot of proteases to degrade the peptide. The person in the art would have expected success in enhancing the potency of the peptide in a biological system by enhancing the stability of the peptide.

## *Conclusion*

NO CLAIM IS ALLOWED.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

```
US-10-204-337A-7
; Sequence 7, Application US/10204337A
; Publication No. US20040128706A1
; GENERAL INFORMATION:
;  APPLICANT: Masliah, Eliezer
;  TITLE OF INVENTION: Method for screening for Anti-Amyloidogenic Properties
and Method for
;  TITLE OF INVENTION:  Treatment of Neurodegenerative Disease
;  FILE REFERENCE: 6627-PC9014
;  CURRENT APPLICATION NUMBER: US/10/204,337A
;  CURRENT FILING DATE:  2002-08-16
;  PRIOR APPLICATION NUMBER: US 60/183,571
;  PRIOR FILING DATE: 2000-02-18
```

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;  PRIOR APPLICATION NUMBER: PCT/US00/07216
;  PRIOR FILING DATE: 2001-03-17
;  NUMBER OF SEQ ID NOS: 15
;  SOFTWARE: PatentIn version 3.1
; SEQ ID NO 7
;   LENGTH: 15
;   TYPE: PRT
;   ORGANISM: Homo sapiens
US-10-204-337A-7

  Query Match             100.0%;  Score 14;  DB 4;  Length 15;
  Best Local Similarity   100.0%;  Pred. No. 3.1e-08;
  Matches   14;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps
0;

Qy          1 DVFMKGLSMAKEGV 14
              ||||||||||||||
Db          2 DVFMKGLSMAKEGV 15

AAY07278
ID   AAY07278 standard; protein; 134 AA.
XX
AC   AAY07278;
XX
DT   06-JUL-1999  (first entry)
DE   Human beta-synuclein.
KW   Human; mouse; synuclein; persyn; diagnosis; neurodegenerative disorder;
KW   cancer; breast; skin; intermediate filament damage.
OS   Homo sapiens.
PN   EP908727-A1.
PD   14-APR-1999.
PF   21-SEP-1998;   98EP-00307628.
PR   19-SEP-1997;   97GB-00019879.
PA   (NEUR-) NEUROPA LTD.
PA   (UYSA-) UNIV ST ANDREWS.
DR   WPI; 1999-217169/19.
PT   New synuclein protein (persyn) and gene, useful in assays for screening,
PT   diagnosing or monitoring cancer, neurodegenerative disorders or skin
PT   disorders.
PS   Disclosure; Page 23; 39pp; English.
XX
CC   This sequence represents the sequence of the human beta-synuclein. The
CC   invention relates to novel human and mouse synuclein family members
CC   designated persyn (AAY07271 and AAY07172). The persyn sequence is useful
CC   for screening, diagnosing or monitoring cancer (especially breast or skin
CC   cancer), neurodegenerative disorders or skin disorders and for
CC   identifying cells having intermediate filament damage
XX
SQ   Sequence 134 AA;

  Query Match             100.0%;  Score 14;  DB 2;  Length 134;
  Best Local Similarity   100.0%;  Pred. No. 5.2e-08;
  Matches   14;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps
0;
```

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Qy          1 DVFMKGLSMAKEGV 14
              ||||||||||||||
Db          2 DVFMKGLSMAKEGV 15


US-09-621-976-4469
; Sequence 4469, Application US/09621976
; Patent No. 6639063
; GENERAL INFORMATION:
;  APPLICANT: Dumas Milne Edwards, J.B.
;  APPLICANT:  Jobert, S.
;  APPLICANT:  Giordano, J.Y.
;  TITLE OF INVENTION: ESTs and Encoded Human Proteins.
;  FILE REFERENCE: GENSET.054PR2
;  CURRENT APPLICATION NUMBER: US/09/621,976
;  CURRENT FILING DATE:  2000-07-21
;  NUMBER OF SEQ ID NOS: 19335
;  SOFTWARE: Patent.pm
; SEQ ID NO 4469
;   LENGTH: 54
;   TYPE: PRT
;   ORGANISM: Homo sapiens
US-09-621-976-4469

  Query Match           100.0%;  Score 7;  DB 2;  Length 54;
  Best Local Similarity   100.0%;  Pred. No. 0.17;
  Matches    7;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps
0;

Qy          1 SMAKEGV 7
              |||||||
Db          9 SMAKEGV 15
```

Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers relating to this application may be submitted to Technology Center 1600, Group 1649 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should

applicant wish to FAX a response, the current FAX number for Group 1600 is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chang-Yu Wang, Ph.D. whose telephone number is (571) 272-4521. The examiner can normally be reached on Monday-Thursday and every other Friday from 8:30 AM to 5:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, Ph.D., can be reached at (571) 272-0867.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CYW
September 25, 2006

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER